TOXIC AND ADVERSE REACTIONS ENCOUNTERED WITH NEW BETA-LACTAM ANTIBIOTICS*

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THE evolution of new beta-lactam antibiotics has been a phenomenon unparalleled in the field of antimicrobial chemotherapy. Stimuli to their development have included economic factors, the emergence of multidrug-resistant microorganisms, and the need for broad spectrum agents less toxic than the aminoglycosides. Although their precise chemotherapeutic role is still to be defined, it is clear that they are generally well tolerated and do not possess the profound, frequently irreversible, oto- and nephrotoxicity associated with aminoglycoside antibiotics.[1-5] This review summarizes the spectrum of adverse reactions seen with the newer beta-lactam agents, the penicillin derivatives mezlocillin, azlocillin, and piperacillin, and the cephalosporin derivatives cefotaxime, cefoperazone, and moxalactam, and compares these reactions to those observed with older penicillin and cephalosporin derivatives (Table 1).

HYPERSENSITIVITY

Hypersensitivity reactions to the newer, extended spectrum penicillins occur with a frequency similar to that of older compounds due to a common 6-amino-penicillanic acid nucleus and a spontaneous, time-dependent *in vitro* degradation to sensitizing derivatives.[6,7] Two to 4% of patients treated with mezlocillin, azlocillin, or piperacillin have experienced late cutaneous eruptions, most of which are maculopapular, non-life-threatening, and IgG or IgM-mediated. This frequency is less than

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TABLE I. ADVERSE EFFECTS OF THE NEW β-LACTAM ANTIBIOTICS

	Cephalosporins	*Penicillins*
Hypersensitivity		
Anaphylaxis	Rare	0.1%
Accelerated reactions	Rare	0.1%
Late rash	1-5%	1-5%
Eosinophilia	2-10%	1-5%
Fever	1%	1-2%
Hematologic		
O Coombs	1-10%	0.1%
Leukopenia	1%	1-3%
Thrombocytopenia	Rare	Rare
Platelet dysfunction	MOX	All
Coagulopathy (PT)	MOX,CPZ,CMN	Rare
CNS		
Seizures	Unknown	Unknown
Renal		
Nephritis	Unknown	Rare
Azotemia	Rare	Rare
Hypokalemia	Rare	1-5%
Gastrointestinal		
Diarrhea	2-15%	1-5%
PMC	1% (CPZ)	Rare
Hepatitis	2-5%	2-5%
Other		
Disulfiram-like effect	MOX,CPZ,CMN	No
Phlebitis	2-10%	2-6%
Superinfection	5-10%	2-5%

MOX=moxalactam, CPZ=cefoperazone, CMN=cefamandole

observed with ampicillin and methicillin because of the high (5 to 10%) frequency of late, nonimmunologic skin reactions seen with these agents, particularly when used in young individuals with coexistant Epstein-Barr virus infection. IgE-mediated, immediate, or accelerated hypersensitivity reactions are significantly less common than late IgG or IgM-mediated reactions, and are reported in 0.01-0.1% of patients as with older agents.

Hypersensitivity reactions observed during administration of cephalosporin derivatives are similar in type but perhaps smaller in magnitude than those observed with the penicillin derivatives.[3,8] This may be related to the greater chemical stability of the cephalosporin nucleus with less tendency to polymerize and to form haptens by opening of the beta-lactam ring. The extent to which immunologic cross-reactions are observed between the newer penicillin and cephalosporin derivatives is not clear, but there appears to be a finite risk of cross-sensitivity due to IgE

antibodies among all beta-lactams.[9] Only 3.8% of patients historically allergic to penicillin experienced hypersensitivity reactions during moxalactam administration [1,10] compared to 2.9% of patients without such a history.

Serum sickness due to immune complexes of antibody (predominantly IgG) and beta-lactam antigen has been seen with older penicillins and cephalosporins[11] but not yet described with limited use of the newer agents reviewed here. Clinical syndromes compatible with serum sickness have been noted with prolonged administration of the second generation cephalosporins cefaclor and cefonicid but detailed immunologic data are not available.

Drug fever is reported in 0.5% to 2% of patients receiving any of the new agents. It may occur with or without rash or eosinophilia, disappears within 24 hours of termination of the drug, and recurs promptly on rechallenge. Fever is produced by release of leukocytic pyrogen, but whether this is mediated by circulating immune complexes or other means is unknown.

Eosinophilia has occurred in 1 to 10% of patients. Comparable prerelease clinical studies suggest that piperacillin and cefoperazone are implicated with greater frequency than other derivatives.[3] The development of eosinophilia is for the most part, however, asymptomatic, reversible, not associated with adverse reactions other than rash, and is related to duration of treatment.[12] Prospective controlled studies undertaken to date have shown no clinically significant differences in the frequency of hypersensitivity reactions between the old and new beta-lactam compounds.[3,12-14]

Hematologic Reactions

Cytotoxic reactions have been occasionally described with penicillin and cephalosporin derivatives as manifested by hemolytic anemia or immune thrombocytopenia. Coombs-positivity, with or without hemolysis, is seen in 0.1% to 0.5% of patients treated with a variety of penicillin derivatives and is usually due to specific IgG antibody directed at the penicillin-red blood cell complex in which penicillin acts as a hapten. It should be anticipated with all penicillin derivatives, and has been described with both mezlocillin and piperacillin.

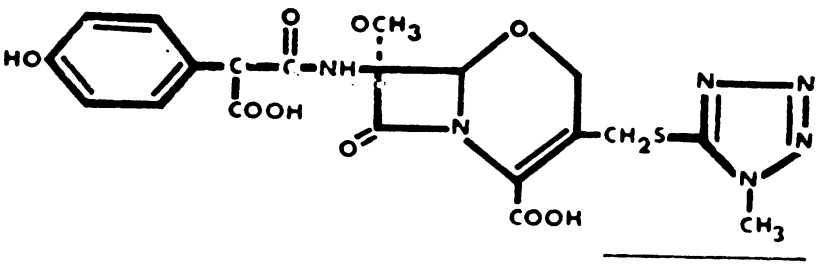
Positive direct Coombs tests are more frequent with cephalosporin derivatives but are due to the red blood cell binding cephalosporin with modification of the cell membrane and nonselective absorption of many plasma proteins, including immunoglobulins, complement, albumin, and

fibrinogen. Hemolysis rarely occurs. The overall incidence of Coombs-positivity in cephalosporin-treated patients has been 1% to 5%, but was 6.4% in patients treated in the prerelease evaluation of cefotaxime.[8] Individual studies of cefotaxime-treated patients have on occasion, however, reported higher rates of 10%[15] and 27%.[16] As with the older cephalosporin derivatives, actual hemolysis has occurred in fewer than 10% of cefotaxime, moxalactam, or cefoperazone-treated Coombs-positive individuals.

Leukopenia has been ascribed to a variety of penicillin and cephalosporin derivatives.[17] It appears dose (>150 mg/kg/d) and time (>7 days) related but its etiology is not clear. Most do not appear to be immunologic or cytotoxic, have no associated eosinophilia or rash, and no accelerated recurrence on rechallenge. Bone marrow aspirates have shown leukocyte precursor maturation arrest or are normal. Leukopenia has occurred in 1 to 3% of patients treated with the newer agents, a frequency similar for most compounds. However, piperacillin appears to cause more leukopenia (2.5%) than azlocillin or mezlocillin (0.5%),[12,18] and up to 15% are reported in one study.[19] Although the latter data have not been confirmed by other investigators, the possible occurrence of severe leukopenia must be appreciated.

Thrombocytopenia has rarely been observed from administration of penicillin and cephalosporin derivatives, including the newer agents. It is probably immunologic, mediated either by cytotoxic antibody directed against the drug-platelet combination or by an "innocent bystander" effect of immune drug-antibody complex absorption onto the platelet surface resulting in platelet activation. In contrast to the rarity of thrombocytopenia, thrombocytosis was common in the early clinical trials of moxalactam, cefotaxime, and cefoperazone, occurring in up to 30% of patients. Recent work indicates that this rise in platelet count is an acute phase reactant and parallels the rise in sedimentation rate or fibrinogen seen in other acute illnesses. Similar thrombocytosis occurs in acute myocardial infarction, postoperative states, and acute infectious diseases treated with non-beta-lactam agents.[20]

Bleeding disorders associated with administration of the new agents have only recently been appreciated.[21] Platelet dysfunction occurs with all penicillin derivatives in a time and dose (blood level) dependent fashion. Originally documented with carbenicillin and ticarcillin,[22] it occurs similarly but less profoundly with piperacillin[23] and mezlocillin.[24] Decreased platelet aggregation, particularly in response to adenosine diphosphate



The structure of Moxalactam. A methyl-tetrazol-thiomethyl group is present at position 3 of the thiazolidine ring (underlined).

(ADP), epinephrine, or arachidonic acid, together with clinical prolongation of the template bleeding times, is due to penicillin binding to platelet surface receptor sites, which prevents effective aggregation and decreases the interaction between platelet surface and its usual activating agents. Clinical bleeding has rarely been reported except with carbenicillin (an incidence of 1 to 2%), but the potential for hemorrhage is clearly high, particularly in the presence of other predisposing factors for bleeding such as uremia, fresh surgical or mucosal wounds, hypoprothrombinemia, or administration of other antiplatelet drugs (e.g., aspirin). Moxalactam has also been shown to inhibit ADP-dependent platelet aggregation [25,26] and to prolong the bleeding time whereas other third generation cephalosporins do not. This may be related to the presence of a carboxyl group on the acyl side chain, also possessed by carbenicillin and ticarcillin.[27]

Subsequent to the introduction of cefamandole, physicians noted that coagulopathy frequently accompanied its use.[28] It recently has been shown that other cephalosporin derivatives possessing a methyl-tetrazol-thiomethyl group at position 3 of the thiazolidine ring (figure) can produce a similar coagulopathy. These drugs include moxalactam, cefoperazone, and cefmenoxime. Coagulopathy is manifested by hypoprothrombinemia due to the inhibition of microsomal vitamin-K-dependent carboxylase by the tetrazol side chain resulting in prolonged prothrombin times.[27] This etiology is probably more important than earlier theories that account for hypoprothrombinemia by suppression of gut flora synthesis of vitamin K. Other compounds, such as ceftriaxone, which are highly excreted in the bile and profoundly influence bowel flora[29] but do not possess the methyl-tetrazol-thiomethyl side chain, have not been shown to produce hypoprothrombinemia.

The frequency with which clinically significant hypoprothrombinemia occurs is hotly debated. In one study,[30] serious bleeding occurred in three

TABLE II. RISK FACTORS FOR BLEEDING EPISODES ASSOCIATED WITH MOXALACTAM ADMINISTRATION

	Total MOX treated (7253)	*Total MOX bleeding (158)*
Renal disease	10%	50%
Age >60	30%	57%
Malignancy	19%	37%
Liver disease	20%	54%

of 42 patients treated with moxalactam but in another study[31] of 100 patients, neither bleeding nor hypoprothrombinemia was observed. Other reports suggest that coagulopathy occurs regularly with both moxalactam and cefoperazone.[21,32-35] Although only 2.2% of moxalactam-treated patients experienced bleeding episodes,[36] 15% (105 of 731) developed hypoprothrombinemia. Two thirds of these episodes were directly related to moxalactam therapy.[27]

Other factors (Table II) in addition to moxalactam or cefoperazone administration may accelerate the development of hypoprothrombinemia or may precipitate bleeding, particularly since hypoprothrombinemia does not develop in healthy volunteers with a normal vitamin K intake. Malnutrition, total parenteral nutrition (without supplemental vitamin K), liver disease, or warfarin administration readily precipitate or exacerbate hypoprothrombinemia. Concomitant platelet dysfunction (aspirin or nonsteroidal anti-inflammatory drug administration, azotemia, sepsis, concomitant penicillin administration), age over 60 years, or fresh mucosal or surgical wounds have the additional potential to precipitate bleeding in such patients.[36]

CENTRAL NERVOUS SYSTEM REACTIONS

Myoclonic jerks and seizures have been produced by many penicillin derivatives administered in high doses, particularly in the presence of renal insufficiency.[37] Despite remarkably high cerebrospinal fluid and serum concentrations, the third generation cephalosporins, piperacillin and mezlocillin, have not clearly precipitated seizures. One patient had an unexplained convulsive episode while receiving azlocillin, but its failure to recur despite continued administration of azlocillin raises doubts about its relationship to the drug.[18] Nevertheless, seizures remain a potential adverse reaction for all these agents.

Renal Adverse Reactions

Interstitial nephritis has occurred with a variety of penicillin and cephalosporin derivatives. Immunologic in origin, it may recur if one penicillin or cephalosporin is substituted for another. Although not yet documented with any of the new agents, its occurrence should be anticipated.

Distinct from allergic interstitial nephritis, tubular dysfunction has been associated with large doses of intravenously administered cephaloridine. Although occasional instances of transient azotemia have been observed,[3,12,18] no definite nephrotoxicity has been described with any of the newer cephalosporins or penicillins.

Cefoxitin can produce "pseudoazotemia" by interference with the laboratory assay for creatinine.[38] However, similar falsely elevated creatinine values are not produced by cefotaxime or moxalactam.[39]

Electrolyte derangements commonly occur with carbenicillin and ticarcillin due to renal tubular effects of the nonreabsorbable divalent cation resulting in hypokalemia alkalosis.[40] The incidence of hypokalemia in prerelease clinical studies of mezlocillin, azlocillin, and piperacillin was 0.7%, 0.5%, and 4% respectively[12,18,41] compared with published frequencies for ticarcillin and carbenicillin of 5% to 15%. However, prospective randomized studies comparing the newer and older penicillin derivatives[12,14] have shown no difference in the incidence of hypokalemia. Monosodium salts of the newer penicillin derivatives provide less sodium (approximately 2 mEq/g) than ticarcillin or carbenicillin (approximately 5 mEq/g) and should present less difficulty for the patient with congestive heart failure. Neither hypokalemia nor sodium load have proven to be a problem with the cephalosporins.

Gastrointestinal Reactions

Diarrhea is a well-recognized adverse effect of most antimicrobial agents. Between 1 and 5% of patients receiving the new beta-lactam compounds have some form of diarrhea, and pseudomembranous colitis has occurred with many of them.[3,33,34,42-44] Diarrhea seems more frequent with cephalosporin derivatives and, in particular, cefoperazone where up to 20% of patients have diarrhea. Stools positive for *Clostridium difficile* have been reported in 10 to 20% of these diarrheal episodes. This is probably due to the large nonrenal (70%) clearance of cefoperazone with high biliary and bowel concentration of the drug.[2] Ceftriaxone has a similarly high biliary excretion and profoundly effects the bowel flora.[29]

Transient elevation in liver transaminase (SGOT, SGPT) have been reported in 2 to 5% of all patients receiving the new beta-lactams,[3,10,12,15,18,44] less than in several studies of carbenicillin where 10 to 20% of patients had transaminase elevation. In isolated study populations, however, higher frequencies have been reported: 21% (17 of 78) SGOT elevation with piperacillin[14] and 36% (32 of 89) SGOT elevation with moxalactam.[45] All transaminase elevations were reversible and of no major clinical importance.

Miscellaneous Reactions

Phlebitis has occurred with a frequency similar to that of older agents in prospective comparative studies.[3,12-14,45] One study in contrast, however, found that cefazolin produced significantly less thrombophlebitis than cefotaxime.[8]

Cephalosporin derivatives possessing the methyl-tetrazolthiomethyl side chain (cefamandole, moxalactam, cefoperazone and cefmenoxime) (see figure) are capable of producing a disulfiram-like reaction when ethanol is ingested by patients receiving these agents.[3,46-48] The structural similarities of the tetrazol group and disulfiram support the fact that this side chain inhibits acetaldehyde dehydrogenase, leading to accumulation of acetaldehyde. The reaction may occur within 24 hours of initiation and for up to three days after termination of antibiotic treatment. It is characterized by rapid onset of flushing, tachycardia, sweating, nausea and vomiting, dyspnea, and confusion. Appropriate instruction regarding alcohol ingestion is therefore necessary when administering any of these compounds.

Superinfections occur with the use of all of antimicrobial agents and are most frequently seen after long courses of treatment, in postoperative patients, patients with chronic respiratory disease, and those with indwelling devices such as endotrachael tubes or bladder catheters. Pseudomonas, enterococcus, and Candida species commonly cause superinfection (2 to 10%) in cephalosporin-treated patients.[16,31,33,43,49] The emergence of enterococcus as a significant pathogen is a particular feature of the newer cephalosporins, especially moxalactam.[45,50,51] Development of resistance has also been observed with these agents, especially during treatment of infections due to *Pseudomonas aeruginosa, Enterobacter cloacae,* and *Citrobacter freundii.*

Conclusion

Coagulopathy, disulfiram-like reactions, and the propensity to superinfection with enterococci are usual occurrences attributable to the molecular

structure and *in vitro* activity of the new cephalosporins. The penicillins, in contrast, appear to possess no new or unique toxicity and the frequency of adverse reactions is similar to that reported for older derivatives. Neither ototoxicity nor nephrotoxicity was observed with any of the new agents, and reactions reported have been, in general, mild and reversible.

Hypersensitivity, positive Coombs test, leukopenia, central nervous system reactions, renal and electrolyte disturbances, gastrointestinal reactions, and thrombophlebitis (Table I) occur with a frequency similar to or less than that reported with older derivatives in the same class. Hypokalemia and platelet dysfunction appear to occur less commonly with mezlocillin and azlocillin than with carbenicillin and ticarcillin. Piperacillin has been associated with a greater incidence of leukopenia and diarrhea than either mezlocillin or azlocillin, but the consistency of these differences is not yet clear. Carbenicillin produces significantly more transaminase elevation than any of the newer penicillins but all instances are mild and reversible. Diarrhea has been reported more commonly with cefoperazone than with the other agents but the possible occurrence of antibiotic-associated colitis should be appreciated with all these compounds.

The only serious adverse reactions attributable to the new beta-lactam antibiotics appear to be the coagulopathies produced by moxalactam and cefoperazone. Hypoprothrombinemia may be manifested by clinical bleeding particularly if additional risk factors for bleeding such as azotemia, age over 60 years, carcinoma, or concomitant liver disease are present. However, even these reactions are preventable through physician awareness and the administration of prophylactic vitamin K. Ten milligrams administered twice weekly, either orally or parenterally, will provide enough Vitamin K to prevent hypoprothrombinemia. Similarly, disulfiram-like reactions can be prevented by patient education.

Superinfection and the emergence of resistance during treatment occurs with many antimicrobial agents and is not readily prevented. The overall incidence is not appreciably greater with these new agents but the offending pathogens may be unique, particularly for the cephalosporins. Pseudomonas, Enterobacter, and enterococcus have proven to be particular problems. Although some of these episodes may be unavoidable, their comprehension should allow us to anticipate complications during treatment with these new agents so that they may be used as a tool for patients' benefit and not a confounding agent in their illness.

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